

Megestrol

Brand Name: Megace, Megace ES

Drug Class: Opportunistic Infection and Other Drugs



Drug Description

Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone, progesterone. [1]

HIV/AIDS-Related Uses

Megestrol acetate was approved by the FDA on September 10, 1993, for use in the management of anorexia, cachexia, and unexplained substantial weight loss in patients with HIV and AIDS. The FDA has designated it an orphan drug for this use. [2] [3]

In clinical trials, megestrol acetate in 800 mg daily doses experienced appetite and weight gain, despite caloric intakes similar to those of control groups. Weight gain was associated with nonwater body weight. HIV patients also reported subjective improvement in their sense of well-being during megestrol therapy. [4]

Non-HIV/AIDS-Related Uses

Megestrol acetate is used in palliative management of recurrent, inoperable, or metastatic endometrial or breast carcinoma. Megestrol acetate is also used as an adjunct to surgery or radiation. Megestrol acetate is not currently recommended for use in other neoplastic disease, but additional studies are underway. [5]

Pharmacology

Megestrol-induced weight gain is likely related to the drug's appetite-stimulant and/or metabolic effects. Megestrol and/or its metabolites may either directly or indirectly stimulate appetite, resulting in weight gain, or may alter metabolic pathways via interference with the production or action of mediators such as cachectin (a hormone that inhibits adipocyte lipogenic enzymes). [6]

Although the precise mechanism of megestrol acetate's antineoplastic action against endometrial cancer is unknown, inhibition of pituitary gonadotrophin production and resulting decrease in estrogen secretion may be a factor. Megestrol

acetate's antineoplastic action on breast carcinoma is caused by modifying the activity of other steroid hormones and by exerting a direct cytotoxic effect on tumor cells. Megestrol acetate decreases the number of hormone-dependent human breast cancer cells and also modifies the stimulatory effects of estrogens on these cells. [7]

The drug is well absorbed from the gastrointestinal (GI) tract; peak plasma concentrations (C_{max}) of the drug were obtained in 1 to 5 hours. Following daily single 800 mg doses of megestrol acetate to cachectic AIDS patients, steady-state C_{max} on day 21 occurred 5 hours after administration and averaged 753 ng/ml. [8]

Megestrol acetate oral suspension is in FDA Pregnancy Category X; the tablet form is in Category D. The drug may cause fetal harm when administered to a pregnant woman. Although there have been no adequate or well-controlled studies in pregnant women, results from studies in pregnant rats given high doses of megestrol acetate showed decreased fetal birth weight, fewer live births, and reversible feminization of some male fetuses. [9] [10]

Progestins, including megestrol acetate, are distributed into breast milk. [11] Because of the potential for transmission of HIV from the mother and for serious adverse effects from megestrol acetate to the breast-fed infant, women should be instructed not to breast-feed while taking megestrol acetate. [12]

The drug is completely metabolized in the liver to free steroids and glucuronides of steroidal metabolites. The major route of elimination appears to be urinary excretion. Following oral administration of radiolabeled megestrol acetate, about 66% of the dose was excreted in urine and about 20% was excreted as feces within 10 days. [13]

Adverse Events/Toxicity

Because of increased genital abnormalities caused by progestins in male and female fetuses, the manufacturer states that megestrol acetate is not

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Adverse Events/Toxicity (cont.)

recommended during pregnancy. Women of childbearing potential who are receiving megestrol acetate therapy should be advised not to become pregnant and to use an effective form of contraception while receiving the drug.[14]

Megestrol acetate is usually well tolerated. Adverse reactions occurring in more than 5% of patients include diarrhea, flatulence, nausea, vomiting, impotence, decreased libido, rash, and hypertension. Hypertension has been reported to resolve following initiation of diuretic therapy or adjustment of patient's pre-existing antihypertensive regimen.[15]

Postmarketing reports associate megestrol acetate with thrombophlebitis, pulmonary embolism, glucose intolerance, and diabetes mellitus.[16]

Pneumonia has been reported in 2% of patients receiving megestrol acetate for AIDS-related cachexia. Nervous system effects reported in patients receiving megestrol acetate for AIDS-related cachexia include insomnia, headache, asthenia, paresthesia, confusion, seizure, depression, neuropathy, hypesthesia, and abnormal thinking. Other adverse effects reported among patients being treated for AIDS-related cachexia include fever, anemia, leukopenia, hepatomegaly, abdominal pain, infections, candidiasis, herpes, pruritus, vesiculobullous rash, sweating, skin disorders, amblyopia, increase in LDH, and sarcoma.[17]

Drug and Food Interactions

Pharmacokinetic studies show that there are no significant alterations in the pharmacokinetic parameters of zidovudine or rifabutin that would warrant dosage adjustment when megestrol acetate is coadministered. The effects of zidovudine or rifabutin on the pharmacokinetics of megestrol were not studied.[18]

Contraindications

Megestrol acetate should not be used in individuals with a history of hypersensitivity to megestrol acetate or to any component of the formulations. In

addition, it should not be used during pregnancy or while nursing. It is contraindicated as a test for pregnancy.[19]

Clinical Trials

For information on clinical trials that involve Megestrol, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Megestrol AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[20]

Dosage Form: Oral suspension containing micronized megestrol acetate 40 mg/ml.[21]

Concentrated oral suspension containing megestrol acetate 125 mg/ml.[22]

Tablets containing megestrol acetate 20 or 40 mg.[23]

Storage: Store tablets in well-closed containers at less than 40 C (104 F), preferably between 15 C and 30 C (59 F and 86 F).[24]

Store oral suspension in tight containers at 25 C (77 F) or less.[25]

Store concentrated oral suspension between 15 C and 25 C (59 F and 77 F), dispense in a tight container, and protect from heat.[26]

Chemistry

CAS Name: Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-[27]

CAS Number: 595-33-5[28]

Molecular formula: C₂₄H₃₂O₄[29]

C₇₄.97%, H₈.39%, O₁₆.64%[30]

Molecular weight: 384.51[31]

Melting point: 214-216 C[32]

Physical Description: White crystalline solid.[33]

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Chemistry (cont.)

Solubility: 2 mcg/ml in water (37 C); 24 mcg/ml in plasma.[34]

Further Reading

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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